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REVIEW ARTICLE

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How COVID-19 can cause autonomic dysfunctions and postural orthostatic syndrome? A Review of mechanisms and evidence

Mehran Hassani[1] | Ali Fathi Jouzdani[1] | Sara Motarjem[1] | Akram Ranjbar[2] | Nakisa Khansari[3]

[1]Neurosurgery Research Group (NRG), Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran

[2]Department of Pharmacology and Toxicology, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran

[3]Department of Cardiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

Correspondence
Nakisa Khansari, Farshchian Cardiovascular Hospital, Hamadan University of Medical Sciences, Hamadan, 6517838678, Iran.
Email: khansary80@gmail.com

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Abstract

Coronavirus disease 2019 (COVID-19) is a viral disease spread by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Because the recent pandemic has resulted in significant morbidity and mortality, understanding various aspects of this disease has become critical. SARS-CoV-2 can affect a variety of organs and systems in the body. The autonomic nervous system plays an important role in regulating body functions, and its dysfunction can cause a great deal of discomfort for patients. In this study, we focused on the effect of COVID-19 on the autonomic system and syndromes associated with it, such as postural orthostatic syndrome (POTS).

KEYWORDS

Autonomic dysfunction, COVID-19, POTS, SARS-CoV-2, Vagus nerve

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was discovered in December 2019. SARS-CoV-2 was discovered in pneumonia patients in Wuhan, China. SARS-CoV-2 characteristics are similar to those of the Coronaviridae family, and it is thought that SARS-CoV-2 is zoonotic (animal) in origin, originating in bats.[1] SARS-CoV-2 has three known variants worldwide, including the UK variant, the African variant, and the Brazil variant. SARS-CoV-2 spreads between people primarily through droplets and, in some cases, aerosols.[2,3] Surface transmission and asymptomatic SARS-CoV-2-infected people are two other modes of transmission.[4] COVID-19 symptoms can appear 2-14 days after exposure and vary in severity, ranging from mild-to-severe illnesses.[1] Patients may exhibit upper respiratory tract infection symptoms such as sore throat and rhinorrhea.[5] Low-to-high fever, dry cough, dyspnea, fatigue, normal or reduced leukocyte counts, and confirmed pneumonia on chest radiography are clinical signs of SARS-CoV-2 infection.[6] Headache, abdominal pain, dizziness, nausea, vomiting, diarrhea, and skin rashes are less common symptoms of SARS-CoV-2 infection.[7] The symptomatic phases of COVID-19 are specified into four groups, including acute COVID-19 (symptoms up to 4 weeks), ongoing symptomatic COVID-19 (symptoms from 4-12 weeks), post-COVID-19 syndrome (symptoms last for >12 weeks), and long COVID (includes both ongoing symptomatic COVID-19 and post-COVID-19 syndrome). After COVID-19, many patients have developed chronic symptoms in the long-COVID phase. These symptoms were initially focused on the

Hassani and Fathi Jouzdani contributed equally to this work.

acute effects of the virus. These are some of the symptoms and signs including autonomic dysfunctions especially postural tachycardia syndrome (POTS).[8]

1.1 | COVID-19 and Neurological symptoms

For the first time, Beijing Ditan Hospital confirmed a case of viral encephalitis caused by SARS-CoV-2, which attacks the central nervous system (CNS).[9] Genome sequencing confirmed the presence of SARS-CoV-2 in cerebrospinal fluid, supporting the theory that this new pneumonia virus can also cause nervous system damage.[9] Long-COVID syndrome exhibits neurological problems, which includes peripheral neuropathy and autonomic nervous system (ANS) dysfunction.[10] COVID-19 patients can develop neurological symptoms. These symptoms can be divided into two categories. The first group is associated with central nervous system involvement, such as headaches, dizziness, altered mental state, and disorientation, while the second group is associated with peripheral nervous system involvement, such as anosmia and dysgeusia.[11-14] Patients may experience cognitive dysfunction, also known as "COVID fog" or "COVID brain fog," which includes memory loss, inattention, poor concentration, or disorientation.[12] These symptoms can be divided into three categories: direct virus effects on the nervous system, para-infectious or post-infectious immune-mediated disease, and neurological complications caused by COVID-19's systemic effects.[15] Furthermore, systemic toxemia, metabolic disorders, and hypoxia during acute infection are factors that contribute to the development of a reversible brain dysfunction syndrome known as infectious toxic encephalopathy.[16] Acute viral infections, such as those caused by SARS-CoV-2, are a major cause of this disease.[16] COVID-19 patients frequently experience severe hypoxia and viremia, which can result in infectious toxic encephalopathy.[17] Besides that, nearly half of COVID-19 patients have headaches, altered consciousness, and other signs of brain dysfunction, and an autopsy study discovered edema in the brain tissue of COVID-19 patients. According to these findings, COVID-19 may eventually cause infectious toxic encephalopathy.[18] Furthermore, infection with coronaviruses (CoV), particularly SARS-CoV-2, has been linked to cytokine storm syndromes, which may explain CoV's ability to cause acute cerebrobasilar disease (Figure 1).[19] COVID-19-related hypercoagulability, as observed in an autopsy series in which widespread microthrombi and patches of infarction were discovered in some brains, would be expected to increase susceptibility to cerebrovascular events.[20] Some cases of Guillain-Barre syndrome, a neuropathy caused by an immune attack on peripheral nerves, have been identified in COVID-19 patients. The majority of cases displayed classic symptoms of this syndrome, such as demyelination on nerve conduction tests, generalized weakness, and elevated proteins in the CSF in the absence of white blood cells There have also been reports of the Miller-Fisher variant of Guillain-Barre syndrome, which is distinguished by cranial nerve involvement and at least one case of antiganglioside antibodies, indicating an immune attack on the peripheral nerves (Figure 1).[21,22]

1.2 | COVID-19 and Autonomic dysfunction

According to research, COVID-19 has an effect on the autonomic nervous system; so that concepts such as the extended autonomous system (EAS), allostasis, and dyshomeostasis may reflect COVID-19's age-related mortality and the involvement of several organ sites in the disease.[23] One study found that COVID-19 patients had increased parasympathetic activity and autonomic imbalance despite key factors such as age, gender, and comorbidities like diabetes mellitus.[24] COVID-19 and the autonomic system have a complicated relationship. For instance, autonomic dysfunction can be result from autoimmune encephalitis (AE) which is manifested by the symptoms of cardiovascular, sudomotor, and other domains of the ANS.[10] COVID-19's cytokine storm response occurs after sympathetic activation. The anti-inflammatory response, on the other hand, is the result of vagal stimulation.[25] Both sympathetic overstimulation and parasympathetic withdrawal play important roles in the development of discomforts in patients. Some conditions, such as hypertension, type II diabetes mellitus, heart failure, and chronic kidney disease, are associated with increased sympathetic nerve activity, which contributes to COVID-19 infection in many cases.[26-29] The increased activity of the sympathetic nervous system causes catecholamine secretion, increased metabolism of the body, increased blood flow, and increased tension in the person's heart. Simultaneously, the parasympathetic nervous system's effect on the vagal anti-inflammatory reflex decreases, while the rate of release of pro-inflammatory cytokines increases[30-32]; these cytokines are thought to be the cause of the cytokine storm.[33] COVID-19-related autonomic dysfunction can be caused by the virus itself.[34] Immune-mediated syndromes, such as orthostatic hypertension (OH) or POTS, can, however, be linked to autoantibodies,[35] which include α-/β-adrenoceptors and muscarinic receptors.[36-39] One of these dysfunctions is orthostatic intolerance. It includes orthostatic hypotension (OH), vasovagal syncope (VVS), and postural orthostatic tachycardia syndrome (POTS). Tachycardia may coexist with resting or postural hypertension in a patient (Figure 1).[40-42] Aside from previous infections like COVID-19 infection, studies define autoimmune disorders in POTS.[43] An abnormal response to standing up is the primary pathophysiology factor of orthostatic intolerance.[44] In a healthy person, baroreceptors in the heart, aorta, and carotid sinus can detect venous return reduction. Standing causes this decrease because more blood flows from the lower body to the heart in this position. The body reacts immediately by increasing sympathetic and adrenergic function (release of epinephrine and norepinephrine). These are the potential causes of tachycardia.[40,44] Tachycardia-related symptoms, such as palpitations, shortness of breath, and chest pain, are caused by the release of epinephrine and norepinephrine. As previously stated, when the sympathetic nervous system is activated, the level of catecholamine rises. An extremely high catecholamine level causes paradoxical vasodilation, sympathetic withdrawal, and parasympathetic nervous system activation via the vagus nerve. This chain of events culminates in hypotension, dizziness, and syncope (Figure 1).[45-48] Hypovolemia

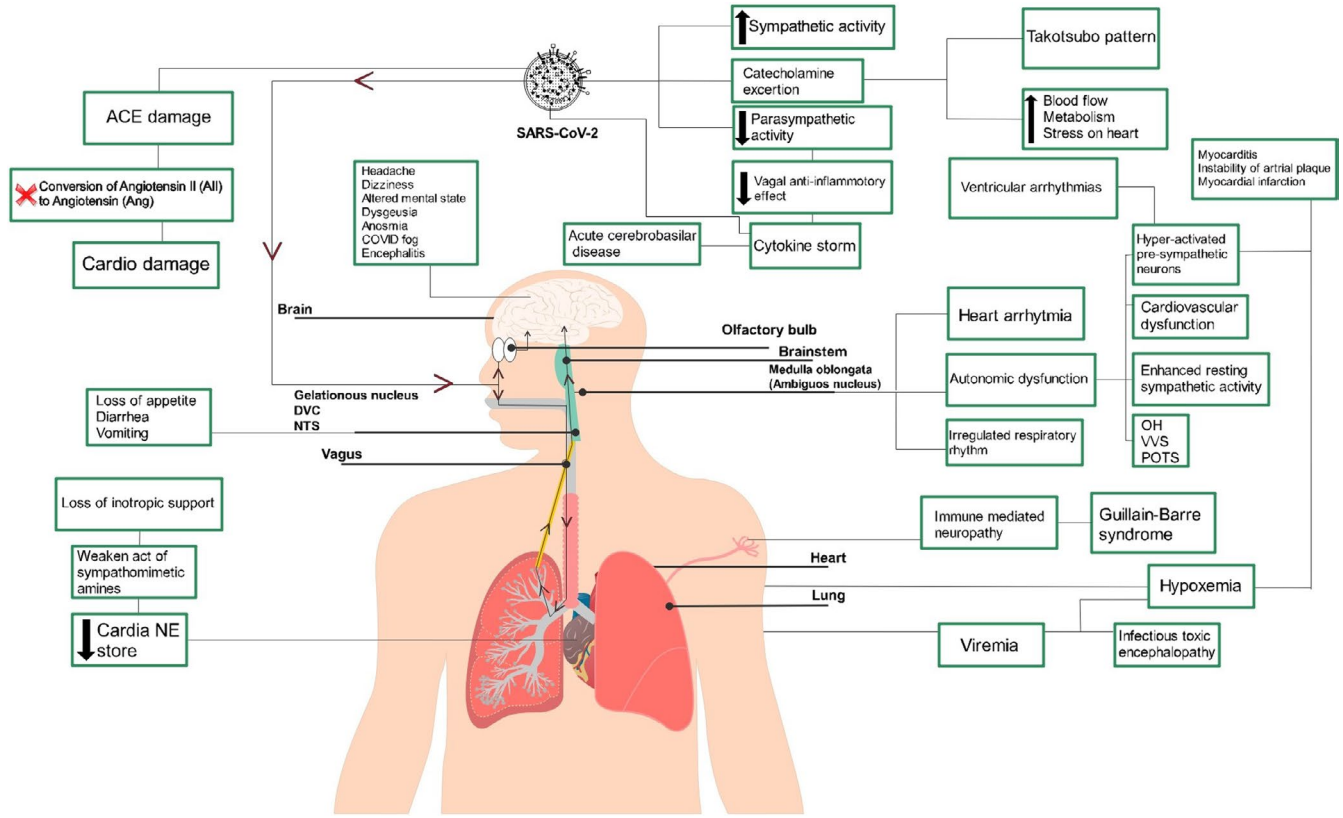

FIGURE 1 SARS-CoV-2 infects the nervous system through the respiratory tract's vagus nerve and olfactory bulbs. Loss of appetite, diarrhea, and vomiting are symptoms of a disorder in the gelatinous nucleus, dorsal vagal complex (DVC), and nucleus tractus solitarius (NTS) of the brainstem. Disorders in the Ambiguous nucleus of the brainstem cause heart arrhythmia, autonomic dysfunction, and respiratory rhythm irregularity. Then, due to autonomic dysfunction, syndromes such as orthostatic hypotension (OH), vaso-vagal syncope (VVS), and postural orthostatic tachycardia syndrome (POTS). Furthermore, autonomic dysfunction is linked to an increase in resting sympathetic activity, cardiovascular dysfunction, and hyperactivated pre-sympathetic neurons. Overstimulated pre-sympathetic neurons are a source of ventricular arrhythmias. Moreover, if it is followed by hypoxemia, myocarditis, arterial plaque instability, and myocardial infarction can be suspected. The capacity of indirect-acting sympathomimetic amines to provide inotropic help is compromised when cardiac norepinephrine (NE) stores are depleted. SARS-CoV-2 disrupts angiotensin-converting enzyme 2 (ACE2) receptors, preventing the conversion of angiotensin II (AII) to angiotensin (Ang) and causing cardio damage. SARS-CoV-2 increases sympathetic activity, which causes catecholamine release, induces catecholamine release, and decreases parasympathetic activity. Catecholamine secretion will activate the Takotsubo pattern, increasing blood flow, metabolism, and stressing the heart. Reduced parasympathetic activity will reduce the vagal anti-inflammatory effect that leads to cytokine storm. Acute cerebrobasilar disease may be caused by a cytokine storm. Hypoxemia and viremia, when combined, are risk factors for infectious toxic encephalopathy. Guillain-Barre syndrome develops as a result of immune-mediated neuropathy. Headache, dizziness, altered mental state, dysgeusia, anosmia, COVID fog, and encephalitis are some of the other neurological symptoms

has been shown to aggravate these syndromes. Hypovolemia can be caused by either initial infection or prolonged bed rest. According to research, prolonged bedrest reduces cardiac output and stroke volume, as well as causes hypovolemia, baroreflex impairment, and sympathetic neural response withdrawal.[49-52]

1.3 | COVID-19 and Vagus nerve dysfunction

Other viruses in the coronaviridae family have been shown to be neuroinvasive and cause neurological disorders. Animal model studies on other respiratory viruses, such as the influenza virus, revealed that the routes of infection are either from the olfactory nerve terminals in the nasal cavity or the vagus nerve in the lungs; as a result, these routes can the source of CNS infection (Figure 1).[53-56] Previously, coronaviridae family viruses such as SARS-CoV-34, 35, or MERS-CoV were found in the brain and particularly in the brainstem.[53] Some respiratory viruses have been shown to enter the brain and affect it by infecting the sensory nerves of the vagus in respiratory organs (Figure 1).[57,58] The vagal nucleus is made up of four nuclei, one of which is the Ambiguous nucleus, which is located in the brainstem's medulla oblongata.[59] Neuron networks in the lower brainstem, specifically ventral to the ambiguous nucleus, the dorsal motor nucleus of the vagus, and the area postrema regulate the basic respiratory rhythm. As a result, SARS-CoV-2 could enter the brain via the vagus nerve. It has the potential to infiltrate the brainstem, particularly the vagal nucleus and its surrounding sites, which play critical roles in

controlling respiratory rhythm, resulting in respiratory dysfunction.[60] According to the cardiovascular and respiratory networks of the brain are intertwined in the brainstem, it is critical to note that this invasion may have an impact on other brainstem functions such as autonomic functions or heart rate regulation.[56]

1.4 | COVID-19 and Heart failure

One of the major concerns among COVID-19 patients is heart failure, so that patients with pre-existing cardiovascular diseases are more likely to contract SARS-CoV-2 and develop more severe symptoms through a variety of mechanisms.[23] Local SARS-CoV-2 infection and local immune responses can result in myocarditis.[23] When ACE2 receptors are disrupted, the conversion of angiotensin II (AII) to angiotensin (Ang) is prevented, which may cause damage.[23,61] Takotsubo cardiomyopathy can be caused by endogenous or exogenous catecholamine toxicity. Endothelial or microvascular dysfunction, as well as coronary arterial plaque instability, may be observed.[62] Heart failure causes a decrease in cardiac norepinephrine stores.[63] This is most likely due to a greater release of norepinephrine with the outflow of neuronal reuptake compared to catecholamine biosynthesis by tyrosine hydroxylase.[64] Reduced norepinephrine (NE) stores in the failing human heart impair the ability of indirect sympathomimetic amines to provide inotropic support.[65] The involvement of the autonomic nervous system (brainstem and hypothalamus) in a viral infection caused dysfunctions in vital organs, including the cardiovascular system.[24] Furthermore, virus infection can have an impact on the cardiovascular system, resulting in myocardial infarction, myocarditis, and arterial and venous thrombosis.[24] It has been established that there are links between renin-angiotensin system (RAS) activation and autonomic dysfunction in cardiometabolic diseases (such as hypertension, heart failure, and diabetes); this relationship frequently manifests itself as a positive feedback loop between RAS activation and tonic increases in efferent sympathetic nerve activity. Increased sympathetic activity activates RAS, which then upregulates sympathetic activity.[27] Medications that block this positive feedback loop can help to reduce the inflammation and autonomic dysfunction associated with these diseases, as well as the morbidity associated with COVID-19.[33] Hyper-activation of brainstem pre-sympathetic neurons and increased sympathetic nerve activity create a pro-arrhythmic substrate in hypertension and heart failure, leading to an increase in ventricular arrhythmias. COVID-19 patients with pre-existing conditions with excessive sympathetic activity (ie, hypertension, diabetes, and heart disease) may be more vulnerable to lethal cardiac arrhythmias due to heightened sympathetic activity combined with COVID-19-induced hypoxemia and inflammation. Patients with COVID-19 may have poorer outcomes as a result of this cycle.[27] When increased resting sympathetic activity (as in hypertension, diabetes, and cardiac disease) is combined with hypoxemia, the patient's heart is thought to be put under more stress, leading to dysfunction and possibly viral myocarditis.[33] Increased heart workload and decreased arterial oxygen, on the other hand, may result in a lack of cardiac tissue complement, exacerbating the pro-arrhythmic substrate.[33]

1.5 | COVID-19 and gastrointestinal symptoms

COVID-19 patients with digestive symptoms require more time to reach the hospital than patients who do not have digestive symptoms.[66] Symptoms such as nausea and vomiting can be critical because they can be caused by disruptions in the central regulation of food intake and impairments in the brain structure involved in the control of vomiting and nausea. Also, in the early stages of infection, there will be a loss of appetite.[67] These structures are found in the dorsal vagal complex (DVC), which is located in the medulla oblongata, the brainstem's lowest part. DVC regulates several important autonomic functions, including heart function, breathing, and food intake. As a result, disorders associated with this region can result in homeostasis dysfunction.[67] The nucleus of the tractus solitarii (NTS) of the DVC, which collaborates with the hypothalamus to regulate food intake, is an important area in food intake regulation.[67] The NTS nucleus and its sub nucleus cause respiratory failure (ie, gelatinous nucleus). As a result, if the NTS is damaged, it may result in a functional change as food intake regulation.[67] Loss of appetite is predicted when the hypothalamus and DVC lose crosstalk during stress.[68] This process alters orexigenic/anorexigenic neuropeptide signaling, which may explain appetite loss.[67] NTS and DMV, on the other hand, are responsible in the brainstem for controlling gastrointestinal tract motility and secretion via neuronal projections.[69] Dysfunction of these brainstem areas can result in digestive symptoms such as abdominal pain, diarrhea, and vomiting.[69] NTS receives afferent neurons from the gastrointestinal tract and has neuronal connections to brain areas (including the amygdala, insula, and anterior cingulate cortex), which may explain nausea [69]. As ACE2 expression and virus titers are high in the oropharyngeal region, SARS-CoV-2 can spread through the axons of the facial nerve, the glossopharyngeal nerve, and the vagus nerve. Because these nerves relay in NTS, they can cause NTS inflammation. This can result in a cytokine storm due to faulty relay of the cholinergic anti-inflammatory pathway and the hypothalamic-pituitary-adrenal axis (HPA). Confirmation will require autopsy studies of the target sites in the brain.[42,70,71]

1.6 | COVID-19 and Postural orthostatic tachycardia syndrome (POTS)

Acute COVID-19 involves several abnormalities in the central nervous system, including stroke, encephalopathy, encephalitis, anosmia, headache, nausea, and delirium. Studies from past SARS and Middle East Respiratory Syndrome epidemics show high levels of confusion, depression of humor, anxiety, memory impairment, and sleeplessness.[72] POTS patients often report viral diseases of the recent past.[48] POTS is most common in young adults aged 15–25.

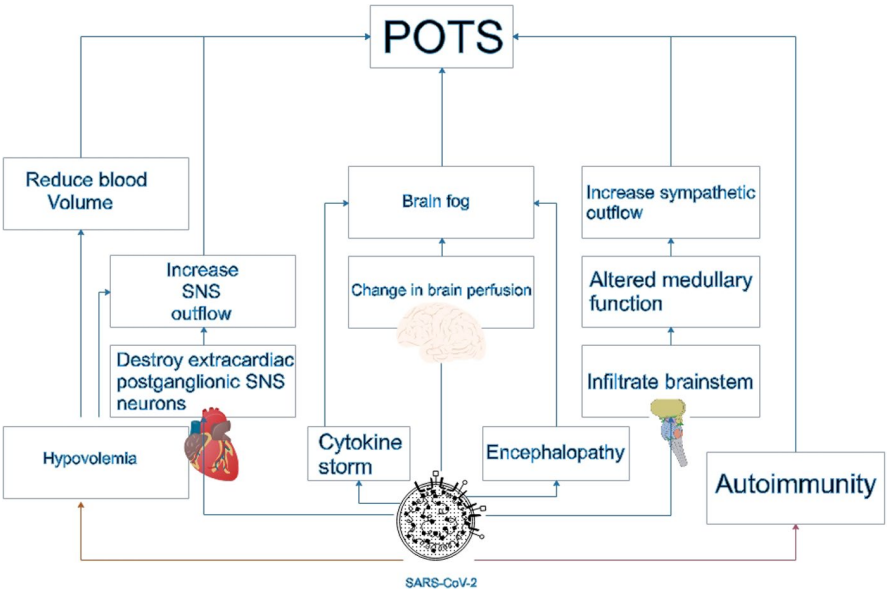

FIGURE 2 SAR-CoV-2 Mechanisms and POTS; As illustrated in the Figure 2, the SARS-CoV-2 can cause POTS either directly by affecting various organs such as the brainstem, brain, heart, and neurons of the heart sympathetic system, or indirectly by causing autoimmunity and hypovolemic

Up to 50% of cases have a history of viral disease, and 25% have a family history of similar symptoms.[73,74] POTS causes differ from person to person, and researchers are still baffled as to the cause of this disease; when a patient sits or tilts their head up for at least 10 minutes and their heart rate exceeds 30 beats per minute, they have POTS syndrome. POTS is diagnosed only after the possibility of orthostatic hypotension, dehydration, heart problems, adrenal insufficiency, epilepsy, Parkinson's disease, and other disorders with similar symptoms has been ruled out. POTS symptoms are nearly always characterized by cerebral hyperfusion and sympathoexcitation.[75] The first symptom is usually an increase in heart rate of more than 30 beats per minute within ten minutes of standing up or tilting the head up. Lightheadedness, blurred vision, cognitive difficulties, and generalized weakness are symptoms of cerebral hypoperfusion; palpitations, chest pain, and tremulousness are symptoms of excessive sympathoexcitation.[73] Other symptoms include severe or long-term fatigue, brain fog, lightheadedness, heart palpitations, nausea and vomiting, headaches, excessive sweating, shakiness, a pale face, and purple discoloration of the hands and legs. POTS patients may experience more than one of these symptoms at the same time.[73] SARS-CoV-2 could infiltrate the brainstem and alter medullary center functions, resulting in increased central sympathetic outflows similar to takotsubo cardiomyopathy; there could be changes in brain perfusion that manifest as brain fog (Figure 2).[76] Hypovolemia is a proposed mechanism in POTS after COVID-19 infection. Fever, anorexia, nausea, excessive nocturnal sweating, and prolonged bed rest may all work together to reduce blood volume while also increasing cardiac SNS outflow (Figure 2). Deconditioning can be part of a vicious cycle in POTS, which also includes low stroke volume, high SNS or SAS outflows, exercise intolerance, and fatigue.[77] SARS-CoV-2 may infect and destroy extracardiac postganglionic SNS neurons, increasing cardiac SNS outflow and eventually leading to neuropathic POTS. Splanchnic venous pooling or a failure of reflexive mesenteric vasoconstriction during orthostasis could be examples of this (Figure 2). SARS-CoV-2 could infiltrate the brainstem and alter medullary center functions, resulting in increased central sympathetic outflows similar to Takotsubo cardiomyopathy. There could be changes in brain perfusion that manifest as brain fog (Figure 2).[76] Autoimmunity plays an important role in POTS following the COVID-19 infection (Figure 2). Immune responses targeting the virus are regulated in a complex, dynamic manner in response to a viral infection, balancing attacking the virus vs attacking the host's own cells. Although there is a substantial body of literature describing autoimmune markers and autoantibodies in POTS, there is insufficient evidence of pathogenicity. Given the survival advantage of viral molecular mimicry and the novelty of COVID-19, POTS could result from disruption of this delicate balance dyshomeostasis.[78] Therapeutic treatments such as increased salt and water intake, ivabradine, H1 and H2 antihistamines, propranolol, and clonidine have been used to treat POTS caused by COVID-19 (Table 1).[78-80]

2 | CONCLUSION

The autonomic nervous system is critical to the body's proper functioning and homeostasis. As previously stated, autonomic system dysfunction can easily affect other systems and organs of the body, such as the respiratory system, cardiovascular system, and gastrointestinal system. Recent research has found a link between SARS-CoV-2 infection and autonomic dysfunction. There have also been some case reports involving autonomic symptoms and syndromes, and the number of them is growing by the day as a result of COVID-19 pandemics.

SARS-CoV-2 pathogenesis could occur through a variety of mechanisms. First of all, SARS-CoV-2 is capable of invading the nervous system. It can enter the central nervous system and areas that control and regulate body functions through respiratory system nerves and olfactory bulbs. As a result, it can infiltrate the nerves

TABLE 1 Summary of case series/reports related to autonomic disorders after COVID-19

	Study	Number of patients	Gender M:F	Age (Range)	PCR/igG test for COVID-19	Post-COVID-19 symptoms	Treatment	Follow-up	Autonomic Dysfunction
1	Kamal Shouman et al 2021[81]	27	9:16	21-77	100% Positive	Autonomic symptoms, lightheadedness orthostatic headache, syncope, hyperhidrosis, burning pain, orthostatic tachycardia, flushing, and weight loss	-	-	2 Pt. SFN exacerbation / 6 Pt. with POTS/14 Pt. OI/ 1 Pt. AAG/ 1 Pt: LBD
2	Blitshteyn and Whitelaw 2021[82]	20	6:14	25-65	30% positive	Tachycardia, shortness of breath, fatigue, panic attacks, anosmia, ageusia, headache, exercise, high blood pressure, chest pain, recurrent fever, dizziness, low blood pressure, presyncope, and weight loss	NPH* for all the patients + other specific treatments for each	Different. Patients were between recovered completely (15%) and stay symptomatic between 2-8 mo (85%)	15 Pt. POTS / 3 Pt. NCS / 2 Pt. OH
3	Johansson et al 2021[79]	3	1:2	28-42	66% positive/33% negative	Myalgia, cough, fever, weakness, dizziness, heat, exercise intolerance, dyspnea, chest pain, vertigo, and brain fog	Increased fluid intake/ ivabradine/ H1 and H2 antihistamines/ Propranolol	One of them remains sick/ two of them are lightly symptomatic and on sick leave	3 Pt. POTS
4	Dani, Dirksen et al 2021[42]	6	0:6	26-50	100% Positive	Gastrointestinal symptoms 5 d prior to symptoms (suspected viral illness), palpitations on standing, dyspnea, fatigue, breathlessness, irritable bowel symptoms, anxiety, aches, dizziness, and Diarrhea,	-	-	2 Pt. POTS/ 4 Pt. OI
5	Miglis et al 2020[78]	1	0:1	26	100% Positive	Continued tachycardia, chest pain, shortness of breath, fatigue, exercise intolerance along with subjective fevers, insomnia, and high blood pressure (to 156/112), orthostatic lightheadedness, and presyncope	Propranolol, clonidine	Patient symptoms have still persisted for 5.5 mo. Couldn't back to work	1 Pt. POTS
6	Miglis et al 2020[80]	1	0:1	36	100% Positive	Fatigue, headache, dizziness, chest pain, low blood pressure, and increased heart rate	Increased salt and water intake, ivabradine	-	1 Pt. POTS

Abbreviations: AGG, autoimmune autonomic ganglionopathy; OH, orthostatic hypotension; OI, orthostatic intolerance; LBD, Lewy body dementia; NCS, nerve conduction study; NPH, non-pharmacological treatment; Pt, patient; POTS, postural orthostatic tachycardia syndrome; SFN: small fiber neuropathy; VVS, vasovagal syncope.

of the autonomic nervous system and cause dysfunction. Second, it may be an autoimmune condition that disrupts the autonomic nervous system's work. Last but not least is the effect of infection on the whole body, which increases tension and induces dysfunction and pain, such as hypovolemia during SARS-CoV-2 infection.

In this study, we tried to demonstrate the relation between COVID-19 and autonomic dysfunction. Some autonomic dysfunction syndromes like POTS are prevalent; however, their origin and treatment are not recognized. This pandemic and accessible patient with this kind of syndromes is an excellent chance to discover more about COVID-19 then try to study more on the autonomic system and its dysfunctions. Finding the mechanisms of these dysfunctions and their treatments certainly helps to improve the quality of patients' life.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ORCID

Ali Fathi Jouzdani https://orcid.org/0000-0002-6838-929X
Nakisa Khansari https://orcid.org/0000-0002-6272-9492

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